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Predictors of Late Cardiovascular Complications in Survivors of Hematopoietic Cell Transplantation

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Abstract

Long-term survival after hematopoietic cell transplantation (HCT) is now an expected outcome. The growing population of survivors is at risk of developing treatment-related complications, including cardiovascular events (CVD). A nested case-control design was used to identify clinical and treatment-related risk factors for development of late (1+ years after HCT) CVD. Cases were identified from a cohort of one+ year survivors transplanted at City of Hope between 1977 and 2006. Controls (HCT survivors without CVD) were matched on age, year of HCT, type of HCT, and length of follow-up. Sixty-three patients with late CVD were identified; 44 (69.8%) with coronary artery events, and 19 (30.2%) with cerebrovascular events. Median age at HCT was 49.0 years; median age at late CVD was 54.0 years; 66.7% had undergone autologous HCT. Multivariate logistic regression analysis revealed multiple cardiovascular risk factors (≥2 of the following: obesity, dyslipidemia, hypertension, and diabetes) after HCT to be associated with a 5.2-fold increased risk of late CVD ($p<0.01$); pre-HCT chest radiation was associated with a 9.5-fold risk of coronary artery disease ($p=0.03$). Pre-HCT exposure to chest radiation and presence of comorbidities are primarily responsible for the risk associated with late CVD after HCT. These data form the basis for developing predictive models for identifying high-risk individuals for targeted surveillance and aggressive management of comorbidities.

INTRODUCTION

Hematopoietic cell transplantation (HCT) is the treatment of choice for many hematologic malignancies. Advances in HCT strategies have contributed to an incremental improvement in survival of 10% per decade;(1) but this improvement is not enjoyed equally by all. A growing population of long-term survivors is at risk of developing treatment-related complications. (2–4) One of the more serious complications is the development of therapy-related cardiovascular disease (CVD).(5,6) Previous reports indicate that cardiovascular events including *cerebrovascular disease* (stroke, transient ischemic attack [TIA], carotid arterial occlusion, symptomatic lacunar infarcts), and *coronary artery disease* (myocardial infarction,

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atherosclerotic heart disease, angina pectoris) are prevalent, and often occur earlier than would be expected in the general population.(3,7,8) Cumulative incidence of CVD approaches 23% at 25 years after HCT in certain high-risk populations, and the incidence appears to increase with time.(8) The risk of CVD is reported to be greatest among allogeneic HCT recipients. (3) Factors such as increasing age, hypertension, diabetes, dyslipidemia, high body mass index (BMI), and male gender are recognized to modify the risk of CVD in the general population. (9,10) HCT survivors are known to be at an increased risk of developing diabetes and hypertension, potentially contributing to the risk of CVD in this population.(3) Finally, HCT recipients are at a 2.3 to 4.0-fold increased risk of death due to cardiac causes when compared with the general population.(11,12) Taken together, these reports provide evidence for the fact that CVD is a significant contributor to post-HCT morbidity and mortality, and that the risk of CVD could potentially be modified by the presence of comorbidities.

However, few studies have conducted a comprehensive evaluation of the risk factors associated with the development of CVD after HCT, and none have evaluated the role of pre-HCT therapeutic exposures. The reports describing this outcome are hampered by small sample size, (3,7,8,13) and the contribution of comorbidities to the risk of CVD among HCT survivors has not been fully explored. The current study addresses these gaps by evaluating the role of pre- and post-HCT therapeutic exposures (chemotherapy, radiation), transplant-related conditioning, and post-HCT comorbidities in the development of CVD in a large cohort of long-term HCT survivors.

METHODS

A nested case-control study design was used. The sampling frame for the cases and controls consisted of a retrospectively constructed cohort of 3,287 consecutive patients who had undergone HCT for hematologic malignancies at City of Hope between 1977 and 2006, and had survived at least one year. A Long-term Follow-up (LTFU) form was completed for all 3,287 patients in this cohort. Information collected on the LTFU form included demographics, disease status, medication, hospitalization, and post-HCT complications including cardiovascular disease, and details regarding graft vs. host disease (GvHD). This information was merged with data from an institutional database on HCT-related exposures such as conditioning and GvHD prophylaxis/treatment. The LTFU form captured information regarding post-HCT complications beginning one year post-transplantation through the date of last contact. Medical records maintained at COH were the primary source of data for completion of the LTFU form. If the date of last medical visit was not recent, or if there were any unexpected gaps in the patients' history within the period of follow-up of interest, a standard protocol was used to identify and contact physicians who were treating patients outside COH to obtain pertinent information. If the physician was not available or unable to provide recent information, the patient was called directly. This method of follow-up ensured that information regarding CVD was captured in an uninterrupted fashion, from one year post-HCT to the date of last contact with a healthcare provider. The human subjects committee at COH approved the protocol. Informed consent was provided according to the Declaration of Helsinki.

To be eligible for consideration as a case, patients were required to have developed CVD (coronary artery or cerebrovascular disease) one or more years after HCT. Multiple controls (one to three) were selected at random from the same cohort and matched to cases for age at HCT (± 5 years), year of HCT (± 2 years), donor source (autologous *v* allogeneic), and length of follow-up (control follow-up exceeded that of matched case).

Exposure variables

For both cases and controls, medical records from COH and other institutions (if indicated) were used to abstract clinical and therapeutic information during the pre-transplantation period, transplantation conditioning, and the post-HCT period. The following data were collected: demographics, disease characteristics, pre-HCT therapeutic exposures (chemotherapy: cumulative dose per square meter body surface area; radiation therapy: total dose, field, and dose per fraction), conditioning regimens (chemotherapeutic agents; total body irradiation [TBI]: number of fractions, and total dose]).

Therapeutic exposures were summarized for cases and controls. Anthracycline cardiotoxicity risk score(14) was calculated by multiplying cumulative dose of each anthracycline (doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone) by a factor that reflects the cardiotoxic potential of each drug and then summing the individual scores; cumulative alkylating agent dose was calculated by multiplying cumulative dose of each alkylating agent (cyclophosphamide, procarbazine, ifosfamide, dacarbazine, busulfan, carmustine, lomustine, and melphalan) by a factor that reflects its acute hematotoxic potential, and again summing the individual scores(15,16) (supplement, Table 1). Chest radiation included mantle (standard and modified), mediastinal, or lung radiation; neck radiation broadly included cervical, parotid, nasopharynx or extended mantle radiation.

Cardiovascular Risk Factors

Comorbidities that developed prior to or after HCT were identified through medical record abstraction. Comorbidities were captured if they were diagnosed by their treating physician and/or if an individual was receiving medications for their management. To be considered as a post-HCT event, the comorbidities had to be diagnosed after the HCT, but before the onset of CVD. Furthermore the comorbidities had to be active at the time of event (cases) or for a comparable period of follow-up (controls).

A separate pre- and post-HCT cardiovascular risk score was calculated by assigning a point for each of the following comorbidities: hypertension, dyslipidemia, diabetes, and obesity (BMI >30 kg/m^2 at HCT) – all well-recognized risk factors for cardiovascular disease.(7,10). A cardiovascular risk score ≥2 was deemed to place individuals at high risk for CVD.(7,10, 17)

Outcome variable: Late Cardiovascular Event

Late CVD events were defined as cardiovascular events developing 1+ years after HCT, and were classified as coronary artery disease (myocardial infarction, angina pectoris, or symptomatic atherosclerotic heart disease [>50% coronary artery narrowing]) or cerebrovascular disease (stroke, TIA, symptomatic lacunar infarct, or symptomatic carotid artery occlusion [>50% narrowing] requiring surgical intervention) per the American College of Cardiology (ACC) established case definitions and clinical data standards for coronary artery and cerebrovascular disease.(18–20) Cerebrovascular events were excluded if they occurred as a result of thrombocytopenia or clotting factor deficiency, were due to central nervous system (CNS) trauma, infection, or due to active CNS disease.

Statistical Analysis

Cases and controls were compared with respect to demographics, pre-HCT therapeutic exposures, HCT-related conditioning, and pre- and post-HCT cardiovascular risk factors, using conditional logistic regression for categorical variables, and linear regression adjusting for matching set for continuous variables. For the purpose of this analysis, primary diagnoses were categorized into two groups: lymphoma (non-Hodgkin lymphoma, Hodgkin lymphoma) and

non-lymphoma (multiple myeloma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other diagnoses).

Multivariable conditional logistic regression was used to identify variables that were significantly and independently associated with CVD after HCT. Variables included were those significantly associated with CVD in the univariate analysis, as well as those thought to impact the clinical outcome, but were not part of the matching criteria. The regression model included gender, ethnicity (non-Hispanic white *v* other), smoking history (never *v* ever), diagnosis (lymphoma *v* non-lymphoma), pre- and post-HCT cardiovascular risk factors (dichotomized as <2 *v* ≥ 2 conditions), conditioning with chemotherapeutic agents (no *v* yes), TBI (no *v* yes), and age at diagnosis (continuous variable). Separate regression models were also created for coronary artery and cerebrovascular disease to identify risk factors that may be unique to these outcomes; for the coronary artery disease model, pre-HCT exposure to chest radiation was added to the model; for the cerebrovascular disease model, pre-HCT exposure to neck and cranial radiation were added. An alpha level of <0.05 was considered significant. Statistical analyses were performed using SAS 9.2 (SAS institute, Cary, NC).

RESULTS

Sixty-three cases with late CVD and 186 matched controls were included in the analysis. Sixty-one cases (97%) had three matched controls. Median follow-up after HCT was 7.3 years (range, 1.3 to 29.8 years) for cases and 8.2 years (range, 1.4 to 30.4 years) for controls; 37% of cases and controls were 10+ year survivors.

Patient Characteristics

Table 1 summarizes the clinical characteristics of cases and controls. Cases were significantly more likely to be male (68.3% *v* 51.6%, p=0.03). There were no significant differences with respect to age at diagnosis, race/ethnicity or underlying diagnosis. Among allogeneic HCT recipients, no differences were observed between cases and controls in terms of the prevalence of acute GvHD, of ever having chronic GvHD, or presence of active chronic GvHD (data not shown).

Therapeutic Exposures

The interval between diagnosis of primary disease and HCT was comparable between cases and controls (Table 2: 1.8 years *v* 1.5 years, p=0.24). There were no significant differences between cases and controls with respect to cumulative anthracycline, alkylating agent, or cisplatin exposure. The proportion of patients exposed to cranial, neck, or chest radiation also did not differ between cases and controls. When data was analyzed separately for coronary artery and cerebrovascular events, pre-HCT exposure to chest radiation was more prevalent among cases with coronary artery disease when compared with controls (11.4% *v* 2.3%, p=0.01); median chest radiation dose was equivalent for both cases (40 Gy, range 24–42) and controls (40 Gy, range 36–40). There were no significant differences in the proportion of patients treated with cranial (8.8% *v* 5.3%, p=0.62) or neck (5.3% *v* 3.5%, p=0.73) radiation among cases with cerebrovascular disease and matched controls, respectively.

Cyclophosphamide (63.1%), etoposide (53.0%), and TBI (53.0%) were the most commonly used conditioning agents. Cases were significantly more likely to have received cyclophosphamide as part of their conditioning regimen when compared to controls (Table 2: 71.4% v 60.2%, p=0.04). There were no significant differences with respect to all other conditioning exposures.

Cardiovascular Risk Factors

Pre-HCT Cardiovascular Risk Factors—Cases were significantly more likely to have been diagnosed with hypertension prior to HCT (25.4% *v* 12.9%; p=0.03) and to have a higher BMI at the time of HCT when compared to controls (28.5 *v* 26.6 kg/m^2; p=0.01); there were no significant differences in the prevalence of other cardiovascular risk factors prior to HCT between cases and controls.

Post-HCT Cardiovascular Risk Factors—Cases were significantly more likely to have hypertension (36.5% v 18.8%; p<0.01), dyslipidemia (33.3 *v* 15.1; p<0.01), and diabetes (20.6 *v* 10.8; p=0.05), as compared with controls with equivalent follow-up (Table 2). Cases were also significantly more likely to have multiple post-HCT cardiovascular risk factors (15.9 *v* 8.1; p<0.01) compared with controls. There were no differences with respect to prevalence of patients on immunosuppressive therapy at the time of cardiovascular risk assessment among cases (52.4%) and controls [(44.4%), p=0.53].

Clinical presentation of late cardiovascular disease

Of the 63 cases with late CVD, 44 (69.8%) presented with clinically documented coronary artery disease (myocardial infarction: n=32, atherosclerotic heart disease: n=9, and angina pectoris: n=3), and 19 (30.2%) presented with cerebrovascular disease (TIA: n=9, stroke: n=7, and symptomatic carotid artery stenosis: n=3). All met clinical diagnostic criteria per the ACC established case definitions and clinical data standards for coronary artery and cerebrovascular disease.(18–20) Median time to CVD was 4.0 years from HCT (range, 1.15 to 19.4 years), and median age at presentation was 54.0 years (range, 25.0 to 82.4 years). None of these cases had clinical evidence of CVD during the first year after HCT.

Of the 63 cases with late CVD, 34 have died. Overall survival following diagnosis of CVD (cases) and comparable follow-up (controls) was significantly worse for cases compared to controls (52.4% v 80.6% at 5 years, p<0.01). For cases, the most common causes of mortality were relapse/progression of primary disease (34.6%), cardiovascular event (30.7%), and infection (15.0%). For controls, relapse/progression of primary disease (69.8%) and infection (12.4%) were the most common causes of death.

Risk factors for Late CVD

As shown in Table 3, multivariate conditional logistic regression revealed that the presence of two or more of the four targeted cardiovascular risk factors (obesity, dyslipidemia, hypertension, and diabetes) were significantly and independently associated with a greater than five-fold (OR=5.2, p<0.01) increased risk of CVD. Furthermore, conditioning with cyclophosphamide trended towards an increased risk of late CVD (OR=2.5, p=0.06).

Coronary artery disease—Multivariable analysis restricted to cases with coronary artery disease and their matched controls revealed pre-HCT exposure to chest radiation (OR=9.5, p=0.03) and presence of multiple post-HCT cardiovascular risk factors (OR=4.8, p<0.01) to be associated with an increased risk.

Cerebrovascular disease—Presence of multiple post-HCT cardiovascular risk factors was associated with a 19.5-fold risk of late cerebrovascular disease (OR=19.5, p=0.02). Neck (OR=0.9, p=0.97) and cranial (OR 0.1, p=0.2) radiation were not associated with an increased risk.

DISCUSSION

The overall goal of this study was to conduct a comprehensive evaluation of the impact of therapeutic exposures (pre-HCT, HCT-related conditioning, and post-HCT) and cardiovascular risk factors on the risk of late CVD in long-term survivors of HCT. To date, few studies have evaluated late-onset coronary artery events or stroke, in part, due to the length and completeness of follow-up necessary to document these outcomes. Our study is the first to incorporate pre-HCT therapeutic exposures, conditioning and post-HCT exposures and comorbidities in creating a comprehensive risk profile for late CVD. We find that, other than a 9.5-fold increased risk of coronary artery disease with pre-HCT exposure to chest radiation, the risk of late-occurring CVD is primarily related to cardiovascular risk factors which develop after HCT.

It is increasingly recognized that atherosclerosis is an inflammatory process, where endothelial injury occurs several years before clinically evident cardiovascular disease.(21–23) While endothelial injury can occur acutely following treatment with high-dose alkylator- or platinum-based chemotherapy, long-term follow-up of non-HCT populations such as Hodgkin lymphoma,(24) breast cancer,(25) and testicular cancer(26) survivors has revealed that the risk of late-occurring CVD is primarily due to exposure to chest radiation and not to systemic chemotherapy. Radiation-induced vascular injury is characterized by endothelial cell proliferation, intimal thickening, medial scarring, lipid deposits and adventitial fibrosis;(27) this process forms the basis for the ensuing atherogenesis and plaque formation in these long-term survivors.(27) In non-HCT populations, the risk of mortality from myocardial infarction after chest radiation ranges from 2.2 to 7.2-fold that of age- and sex-matched controls;(28) the highest risk is observed among those treated at age >21 years, with higher doses of radiation (>40 Gy), and among those treated during the earlier treatment eras (<1985).(24,27,28) In the current study, we demonstrate a 9.5-fold increased risk of coronary artery disease in survivors treated with chest radiation, after adjustment for demographics, treatment era, other therapeutic (pre-HCT chemotherapy, conditioning) exposures, and cardiovascular risk factors. Unlike previous reports,(29,30) we were unable to demonstrate an association between cerebrovascular disease and cranial or neck radiation.

Well-established cardiovascular risk factors such as insulin resistance with compensatory hyperinsulinemia, impaired glucose tolerance, hypertriglyceridemia, hypertension and central obesity are increasingly being reported after HCT.(3,31–34) Dyslipidemia, glucose intolerance, and hypertension can be a consequence of prolonged immunosuppressive therapy following allogeneic HCT, due to exposure to TBI, or due to other conditions such as growth hormone deficiency or hypothyroidism.(6) In conventionally-treated cancer populations, cardiovascular risk factors are known to modify risk of CVD.(24,25,35,36) Dorresteijn(35) and colleagues were one of the first to report an increased risk of CVD in long-term cancer survivors; they demonstrated a twelve-fold increased risk of stroke among head and neck cancer survivors with diabetes or hypertension when compared to survivors without these risk factors, and the magnitude of risk increased with longer follow-up. Subsequent studies in Hodgkin lymphoma(24,30,36) and breast cancer(25) survivors have confirmed that chronic health conditions such as hypertension, diabetes, and dyslipidemia significantly contribute to the increased risk of CVD, even after adjustment for well-recognized demographic (age, gender), lifestyle (smoking history), and therapeutic (ionizing radiation) risk factors. These findings have formed the basis for current recommendations for screening and cardiovascular risk reduction in childhood and adult-onset cancer survivors.(28,37,38)

Few studies have explored this association in HCT survivors. A recent report(8) found the risk of CVD to be higher among allogeneic HCT recipients, and in those with multiple cardiovascular risk factors. In another study limited to allogeneic HCT recipients,(7) older age

at HCT and having multiple cardiovascular risk factors were the only significant predicators of self-reported late cardiovascular events. In the current study, HCT survivors with CVD were significantly more likely to have multiple cardiovascular risk factors, resulting in a greater than five-fold increased risk of CVD. In fact, having a high cardiovascular risk score was associated with a 20-fold increased risk of cerebrovascular complications such as stroke or TIA after HCT.

High-dose cyclophosphamide is commonly used as part of conditioning regimens for HCT. Cardiotoxicity associated with high-dose cyclophosphamide is typically acute, dose-dependent, and ranges from asymptomatic electrocardiographic changes, to pancarditis and congestive heart failure.(6,39) It is unclear whether subclinical myocardial injury sustained during conditioning contributes to acceleration of atherosclerotic disease after HCT. Preliminary studies suggest that patients treated with high-dose cyclophosphamide have higher numbers of circulating endothelial cells immediately following conditioning.(40,41) These endothelial cells may reflect disruption of the micro-vascular bed, leading to accelerated thrombus formation.(40,41) The role of cyclophosphamide-induced endothelial injury in initiating clinically significant CVD years following HCT is not well-defined. In the current study, conditioning with cyclophosphamide was associated with a 2.5-fold higher risk of CVD, an association that approached statistical significance.

Any retrospective review of medical records is limited by the amount of information available for review. As such, we were not able to reliably ascertain information regarding other cardiovascular risk factors such as currency of smoking, or pack-years of tobacco exposure, as well as details regarding physical activity. However, the prevalence of *any* smoking, was equivalent to previous reports from similar populations(24,30) and was included in the final multivariate analysis model. Furthermore, other studies, using self-reported information from a similar population have demonstrated, that the large majority of HCT survivors quit smoking after HCT, with less than 15% reporting current use of tobacco.(7,42) Cases included in this study had clinically overt coronary artery or cerebrovascular disease. The cases did not include those individuals who may have had asymptomatic CVD. The focus of this study was to develop a deeper understanding of the impact of HCT-related exposures and comorbidities on the development of clinically overt cardiovascular events, and as such, asymptomatic cardiovascular disease would not fit this definition.

In summary, pre-HCT exposure to chest radiation and multiple cardiovascular risk factors developing post-HCT are primarily responsible for risk of CVD developing in HCT survivors. While it appears that conditioning with high-dose cyclophosphamide may have contributed to an increased risk, more studies are needed to evaluate the role of conditioning exposures in initiating clinically significant CVD in the post-HCT setting. These data form the basis for developing predictive models for identifying high-risk individuals in order to conduct targeted surveillance, as well as develop preventive strategies in the form of aggressive management of comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of Patient Population and Pre-HCT Exposure

Characteristic	Cases (N=63)*	Controls (N=186)*	*P*-Value
Age at initial diagnosis, years			
Mean (SD)	47.8 (13.0)	47.3 (12.5)	0.69
Gender, No. (%)			
Male	43 (68.3)	96 (51.6)	0.03
Ethnicity/race, No. (%)			
Non-Hispanic white	47 (74.6)	119 (64.0)	0.14
Others	16 (25.3)	67 (36.0)	
Diagnosis, No. (%)**			
Lymphoma	27 (42.9)	67 (36.0)	0.31
Non-Hodgkin lymphoma	23 (36.5)	57 (30.6)	
Hodgkin lymphoma	4 (6.3)	10 (5.4)	
Non Lymphoma	36 (57.1)	119 (64.0)	
Multiple Myeloma	12 (19.0)	43 (23.1)	
Acute lymphoblastic leukemia	4 (6.3)	11 (5.9)	
Acute myeloid leukemia	10 (15.9)	33 (17.7)	
Chronic myeloid leukemia	9 (14.3)	16 (8.6)	
Other	1 (1.6)	16 (8.6)	
Pre-HCT comorbidity, No. (%)			
Smoking, ever	31 (49.2)	75 (40.3)	0.27
Hypertension	16 (25.4)	24 (12.9)	0.03
Dyslipidemia	6 (9.5)	12 (6.5)	0.41
Diabetes	3 (4.8)	9 (4.8)	0.99
Pre-HCT therapy			
Anthracycline, mg/m^2			
Mean (SD)	205.1 (140.9)	177.8 (139.4)	0.18
Alkylating agent, g/m^2			
Mean (SD)	4.2 (7.8)	3.2 (9.6)	0.43
Cisplatin, mg/m^2			
Mean (SD)	60.0 (139.5)	48.4 (121.1)	0.38
Cranial radiation, No. (%)	2 (3.2)	7 (3.8)	0.84
Neck radiation, No. (%)	2 (3.2)	6 (3.2)	0.99
Chest radiation, No. (%)	5 (7.9)	6 (3.2)	0.17

Abbreviations: HCT, hematopoietic cell transplantation; SD, standard deviation.

* Group matching criteria included: age at HCT (+/−5y), type of HCT (autologous vs. allogeneic), year of HCT (+/−2y), duration of follow-up.

** Analyzed as Lymphoma (non-Hodgkin's lymphoma, Hodgkin's lymphoma) vs. Non-lymphoma (Multiple myeloma, Acute lymphatic leukemia, Acute myeloid leukemia, Chronic myeloid leukemia, and other).

Table 2

HCTConditioning regimens and Post-HCT Outcomes

Characteristic	Cases (N=63)*	Controls (N=186)*	*P*-Value
Age at HCT, years			
Mean (SD)	49.6 (13.0)	48.8 (12.3)	
Donor source, No. (%)			
Autologous HCT	42 (66.7)	123 (66.1)	
Time from diagnosis to HCT, years			
Mean (SD)	1.8 (3.6)	1.5 (1.7)	0.24
Body mass index at HCT, Kg/m^2			
Mean (SD)	28.5 (6.4)	26.6 (5.0)	0.01
Conditioning Regimen			
Cyclophosphamide	45 (71.4)	112 (60.2)	0.04
Etoposide	33 (52.4)	99 (53.2)	0.79
Total body irradiation	34 (54.0)	98 (52.7)	0.78
Melphalan	15 (23.8)	60 (32.3)	0.09
Carmustine	10 (15.9)	22 (11.8)	0.46
Busulfan	8 (12.7)	24 (12.9)	0.99
Post-HCT comorbidities			
Hypertension	23 (36.5)	35 (18.8)	<0.01
Dyslipidemia	21 (33.3)	28 (15.1)	<0.01
Diabetes	13 (20.6)	20 (10.8)	0.05
Cardiovascular risk**			
<2 conditions	50 (84.1)	169 (91.9)	
≥2 conditions	10 (15.9)	15 (8.1)	<0.01

Abbreviations: HCT, hematopoietic cell transplantation; SD, standard deviation.

*Group matching criteria included: age at HCT (+/−5y), type of HCT (autologous vs. allogeneic), year of HCT (+/−2y), duration of follow-up.

**Conditions included: Hypertension, Dyslipidemia, Diabetes, Obesity (BMI >30kg/m^2) at HCT

Table 3

Multivariate Analysis of Risk Factors Associated with Late CVD

Risk Factor	Odds ratio	95% CI	*P*-Value
Gender			
Female	1.0		
Male	1.6	0.80–3.21	0.18
Ethnicity			
Others	1.0		
Non-Hispanic white	1.8	0.87–3.68	0.12
Age at diagnosis			
	1.1	0.96–1.17	0.23
Smoking			
Never	1.0		
Ever	1.3	0.67–2.38	0.46
Diagnosis*			
Non-lymphoma	1.0		
Lymphoma	0.8	0.31–1.97	0.60
Pre-HCT cardiovascular risk factors			
< 2 conditions	1.0		
≥ 2 conditions	0.8	0.25–2.65	0.74
Conditioning chemotherapy			
No cyclophosphamide	1.0		
Cyclophosphamide	2.5	0.94–6.66	0.06
Total body irradiation (TBI)			
No TBI	1.0		
TBI	1.0	0.47–2.24	0.94
Post-HCT cardiovascular risk factors			
< 2 conditions	1.0		
≥ 2 conditions	5.2	2.14–12.83	<0.01

*Analyzed as Lymphoma (non-Hodgkin's lymphoma, Hodgkin's lymphoma) vs. Non-lymphoma (Multiple myeloma, Acute Lymphatic Leukemia, Acute Myeloid Leukemia, Chronic Myelogenous Leukemia, and other).